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Health Risk Assessment of Chemical Mixtures

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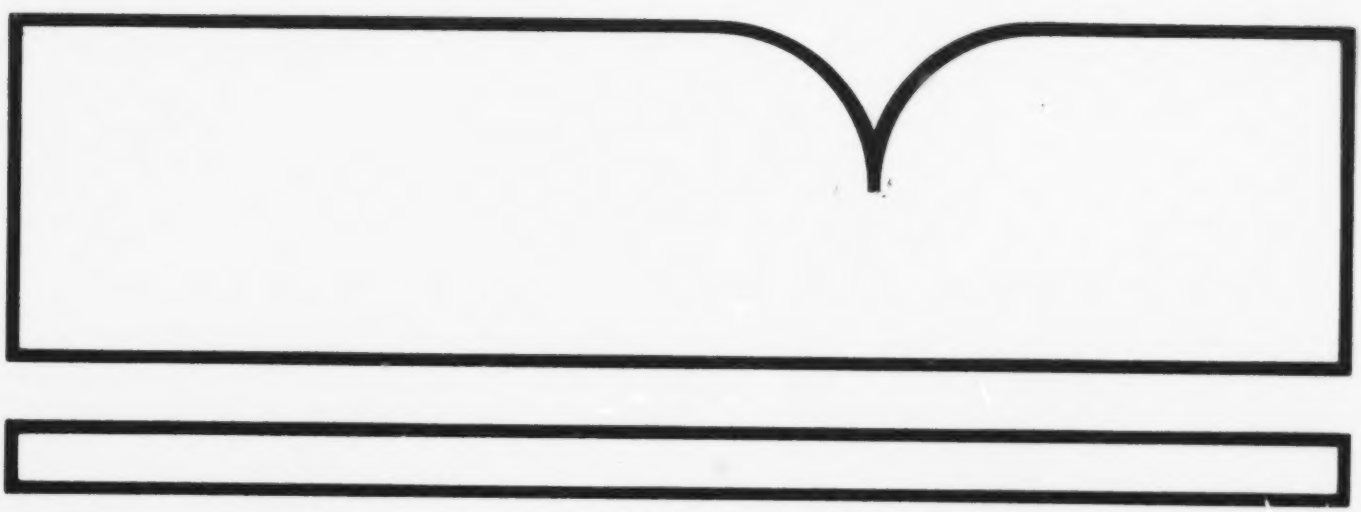

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Health Risk Assessment of Chemical Mixtures

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ABSTRACT

The implementation of Superfund requires a methodology for estimating health risk from multi-chemical contamination at ambient levels. Most often, the chemical composition of these mixtures is poorly characterized, exposure data are uncertain and toxicologic data on the known components of the mixture are limited. However, a potential human health hazard may exist and the U.S. EPA, state and local governments need to be able to assess the total hazard in order to make decisions on appropriate action. This paper describes a procedure for assessing the risks from chemical mixtures that includes options when different kinds of data are available. Good-quality information mation on the mixture of concern or a similar mixture should always be used. A less desirable, but still useful approach, is to utilize data on components and their interations. The quality of exposure and toxicity data must be determined and the uncertainties involved in each risk assessment must be thoroughly discussed. Water contamination is briefly discussed since it is of vital concern as the primary exposure medium for chemical mixtures. The methodology for estimating the human health risk from single chemicals, both carcinogens and systemic toxicants, is reviewed as it forms the basis for the assessment of mixtures.

INTRODUCTION

Public awareness of environmental issues in the U.S. increased dramatically in the 1970s, and was accompanied by continuously expanding scientific investigations of pollution by various toxic chemicals. A new facet was added in the 1980s with the passage of the Comprehensive Environmental Response, Conservation and Liability Act (CERCLA), the so-called "Superfund" legislation. While previous statutes (e.g. Clean Air Act, 1963; Clean Water Act, 1977) were largely focused on hazards due to single chemicals, the Superfund Act required the hazard evaluation of waste sites, that is, the assessment of health hazard from human exposures to mixtures of chemicals.

Since 1979, the staff of the Environmental Criteria and Assessment Office in Cincinnati of the U.S. EPA has been developing health risk assessment guidelines and methodologies to be used in deriving "acceptable daily intakes" or "risk-specific intakes" for environmental pollutants. Specific guidelines for health risk assessment were developed for use in preparing the 65 Ambient Water Quality Criteria Documents, mandated by by the Clean Water Act of 1977 (14,17).

These efforts were directed primarily towards predicting exposure levels for individual chemicals which would be below the theoretical population threshold for adverse effects in the case of systemic toxicants effects, or would estimate an intake for carcinogens corresponding to an upper-bound lifetime risk. Since these methodologies were originally developed to address the issue of water criteria for various toxic species, exposure across the entire lifespan was a basic assumption in these estimates. In addition, there was no necessity for defining risk associated with supra-threshold exposures to non-genotoxic chemicals since the emphasis was the definition of acceptable exposure levels. One of the striking differences between Superfund and the other laws enforced by EPA is that under Superfund, there is a need to estimate the hazard associated with existing contamination levels. Thus, we had to shift from a "protective" to a "predictive" approach in the development of guidelines.

Since Superfund deals with site-specific issues, a new spectrum of risk assessment questions have arisen. In addition to estimates of risk following lifetime exposures, we now must consider the consequences of partial lifetime exposures. In order to evaluate various types of remedial actions, the risk associated with exposures of varied duration at varied levels must be evaluated. In addition, the estimate of risk associated with exposure to multiple chemicals at potentially supra-threshold levels has emphasized the need to consider interactions between constituents. Obviously, the goal of limiting exposure to virtually safe levels still remains. However, definition of existing hazard plays a vital role in determining priorities and in planning remedial actions. In dealing with site-specific situations, many options related to exposure control exist, in contrast to criteria levels where unrestricted lifetime exposure, by necessity, formed a basic premise.

A primary concern in the evaluation of these sites is the potential for migration of site constituents into ground and surface waters. Once this has occurred, options for controlling exposure are severely compromised due to current or potential use of these contaminated waters as drinking water sources. It is then necessary to characterize incremental exposure as a function of site-specific factors; a difficult and highly uncertain endeavor.

In this paper the major emphasis is placed on a review of the approach dealing with health risk assessment of chemical mixtures. The approach of health risk assessment of single chemicals is briefly discussed because it forms the basis of the evaluation of mixtures. The problem of water contamination is briefly discussed since it is of vital concern as the primary exposure medium for chemical mixtures.

WATER POLLUTION

The burning Cuyahoga River in 1969 illustrated a serious nationwide water pollution problem. Water basins in the U.S. have been shown to be polluted by increasingly complex municipal and industrial discharges (2). In addition to the contamination of surface waters in this manner, ground water pollution has recently become a general public concern. About half of the U.S. population uses ground water as its source of drinking water. Ground water from individually-owned wells represents a major drinking water resource in many rural areas. Regionally, the middle West and West use more ground water relative to surface water than other regions (2). Some of these states with high ground water usage (e.g., Nebraska, Kansas, Oklahoma) are also characterized by agricultural activity, increasing the possibility of contaminating ground water sources with pesticides and fertilizers. A more recent and growing public concern is the potential for ground water to be contaminated from hazardous waste disposal sites. Preventing and cleaning up contaminated ground water presents many difficulties not encountered with surface water pollution. Once an aquifer is contaminated, its restoration as a usable drinking water supply is extremely difficult and/or expensive. With an increasing reliance on ground water,

it is important that to be able to identify and characterize the health risk from contaminants in sources of drinking water (16).

SINGLE CHEMICALS: RISK SPECIFIC INTAKE LEVELS AND ACCEPTABLE DAILY INTAKES

Health risk assessment deals with estimates of exposure to environmental pollutants and associated health hazards. Such an assessment includes the basic toxicologic concept of dose-response relationships; for systemic toxicants we compare actual exposure to levels which do not present a human health hazard. For carcinogens, only the incremental risks associated with a pollutant level in a specific environmental medium are considered. In agreement with the National Academy of Sciences (7), EPA assumes that carcinogenesis is a non-threshold phenomenon, whereas other toxic effects have thresholds, i.e., doses below which no adverse effects will occur. As a result, the first step in single chemical risk assessment involves a determination of the potential carcinogenicity of the chemical. Depending upon this determination, the risk assessment proceeds utilizing one of two parallel methodologies which have been designed to address non-threshold or threshold effects.

Carcinogens (Nonthreshold Effects) (15)

After a compound has been determined to have the potential to cause cancer in humans the relationship between risk and exposure is estimated. Two types of data are used for quantitative estimates, human studies where excess cancer risk has been associated with exposure to the agent, and lifetime animal studies.

If human epidemiologic data with sufficiently valid exposure information are available for the compound, the data are analyzed by appropriate statistical procedures which assume a linear dose-response relationship. If the epidemiologic data show no significant carcinogenic effect when positive animal evidence is available, an upper limit of the cancer incidence is calculated, assuming that the true incidence is just below the level of detection in the epidemiologic studies.

Cancer risk assessment for low exposure levels is based on estimates of the cancer potency, i.e., the slope of the dose-response curve in the low dose region. The estimated human potency, is derived directly when adequate epidemiologic data are available. When animal studies must be used, the human potency estimate is calculated using the linearized multistage model fitted to the animal data (3,17). First the upper 95% confidence limit ($q_1^*(A)$) the linear coefficient is determined. Then, $q_1^*(A)$ is adjusted for exposure duration and species differences to give the estimated human potency [in $(mg/kg/day)^{-1}$]:

$$q_1^*(H) = \frac{q_1^*(A)\ (70/W_A)^{1/3}}{(l_e/L_e)\ (L_e/L)^3} \qquad (1)$$

where:

$q_1^*(A)$ = animal potency $(mg/kg/day)^{-1}$
70 = assumed human weight, kg
W_A = animal weight, kg
l_e = length of exposure
L_e = length of experiment or observation period
L = lifespan of the animal.

The cube root of the ratio of body weights is used to adjust for species differences on the assumption that metabolic rate is proportional to body surface area, which is proportional to the 2/3 power of body weight The factor l_e/L_e adjusts the actual dose to a daily dose averaged over the length of the experiment. The third factor, $(L_e/L)^3$, is used to estimate risk from lifetime exposure when the animal experiment is only partial lifetime. This adjustment is necessary to allow for positive responses that would have occurred had sufficient time been allowed for the tumors to develop (17).

After the human potency has been calculated, the intake rate (I, in mg/day) associated with a specific lifetime risk (e.g., 10^{-5} or 1 in 100,00 is determined:

$$I = \frac{70\ (10^{-5})}{\text{potency}} \qquad (2)$$

This risk-specific intake rate is easily converted into a media concentration by dividing by the appropriate intake rates for the exposure medium For example, assuming an intake of 2 l water/day, the risk specific water concentration (C, in gm/l) is:

$$C = \frac{I}{2} \qquad (3)$$

The prediction of cancer risk at a given exposure level uses the same basic approach outlined above, and involves similar assumptions. When huma data are adequate, the observed human potency is used directly to predict the upper bound of risk. When animal data must be used, and particularly when higher exposure levels are involved, the potency alone is not sufficient, and the complete model should be used. The risk (r) at exposure d using the multistage model is (3):

$$r(d) = 1 - \exp(-q_0 - q_1 d - q_2 d^2 - \ldots) \qquad (4)$$

where the q_i's are parameters in the model to be estimated by curve-fitting procedures. The incremental risk (or "excess risk") is then:

$$R = \frac{r(d) - r(0)}{1 - r(0)} \qquad (5)$$

An estimated upper confidence limit on the excess risk R is used as the lifetime risk projection at exposure level d, suitably modified as above for species differences and for duration if the animal study was for only partial lifetime.

Systemic Toxicants (Threshold Effects) (14)

Five types of response levels are considered for deriving criteria based on noncarcinogenic responses:

- NOEL - No-Observed-Effect Level
- NOAEL - No-Observed-Adverse-Effect Level
- LOEL - Lowest-Observed-Effect Level
- LOAEL - Lowest-Observed-Adverse-Effect Level
- FEL - Frank-Effect Level

Adverse effects are defined as any effects that result in functional impairment and/or pathological lesions that may affect the performance of the whole organism or that reduce an organism's ability to respond to an additional challenge. Frank effects are defined as overt or gross adverse (e.g., severe convulsions, lethality).

These concepts are illustrated in Figure 1. They represent landmarks that help to define the threshold region in specific experiments. Thus, if an experiment yields a NOEL, a NOAEL, a LOAEL, and a clearly defined FEL in relatively closely spaced doses, the threshold region has been relatively well-defined. Such data are very useful in deriving Acceptable Daily Intakes (ADIs). On the other hand, a clearly defined FEL is of little use in establishing criteria when it stands alone because such a level gives no indication of how far removed it is from the threshold region. Similarly, a free-standing NOEL has little utility because there is no indication of its proximity to the threshold region.

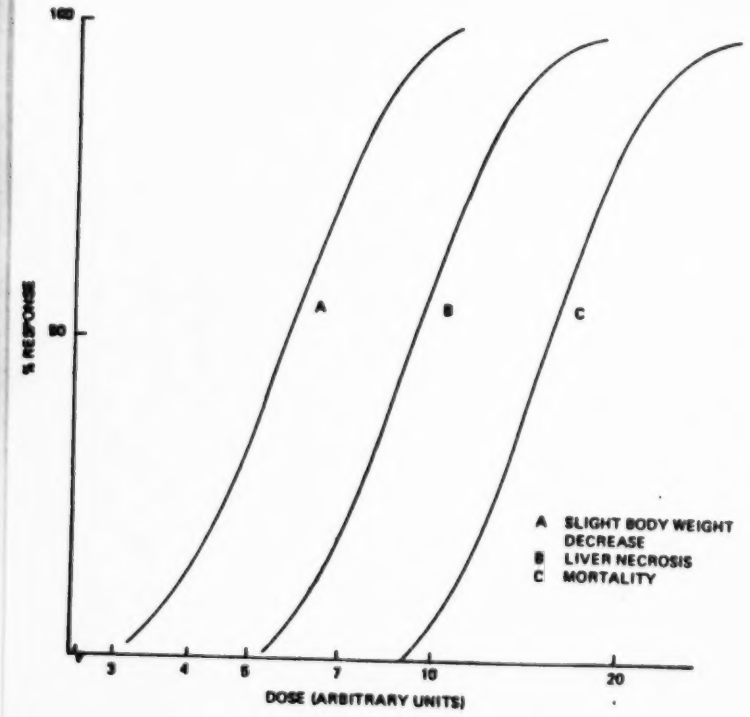

FIGURE 1. RESPONSE LEVELS CONSIDERED IN DEFINING THRESHOLD REGIONS IN TOXICITY EXPERIMENTS. DOSES ASSOCIATED WITH THESE LEVELS ARE AS FOLLOWS: 3 - NOEL, NOAEL; 4 - LOEL, NOAEL; 5 - NOAEL (HIGHEST); 7 - LOAEL; 10 - FEL; 20 - FEL. (14)

Based on the above dose-response classification system, the following guidelines for deriving criteria from toxicity data can be used.

- A free-standing FEL is unsuitable for the derivation of criteria.
- A free-standing NOEL is unsuitable for derivation of criteria. If multiple NOELs are available without additional data on LOEL's, NOAEL's, or LOAEL's, the highest NOEL should be used to derive a criterion.
- A NOAEL, LOEL, or LOAEL can be suitable for criteria derivation. A well-defined NOAEL from a chronic (at least 90-day) study can be used directly, dividing by the appropriate uncertainty factor. For a LOEL, a judgment must be made as to whether it actually corresponds to a NOAEL or a LOAEL. In the case of a LOAEL, an additional uncertainty factor is applied; the magnitude of the additional uncertainty factor is judgmental and should lie in the range of 1 to 10. Caution must be exercised not to substitute Frank-Effect Levels for Lowest-Observed-Adverse-Effect Levels.
- If--for reasonable closely spaced doses--only a NOEL and a LOAEL of equal quality are available, the appropriate uncertainty factor is applied to the NOEL.

In using this approach, the selection and justification of uncertainty factors are critical. The National Academy of Science (7) has provided guidelines for using uncertainty factors. "Safety factor" or "uncertainty factor" is defined as a number that reflects the degree or amount of uncertainty that must be considered when data from animal experiments are extrapolated to humans. When the quality and quantity of experimental data are satisfactory, a low uncertainty factor is used; when data are judged to be inadequate or equivocal, a larger uncertainty factor is used. In those cases where the data do not completely fulfill the conditions for one category--or appear to be intermediate between two categories--an intermediate uncertainty factor is used. Such intermediate uncertainty factors may be developed based on a logarithmic scale. These issues were reviewed by Dourson and Stara in 1983 (5). In order to determine the acceptable exposure level in water, the highest NOEL or NOAEL, or the lowest AEL (depending on the data available) is divided by one or more uncertainty factors (17). The ADI is then substituted for I in equation 3 above.

APPROACH TO TOXICITY DATA EVALUATION

For the purposes of projecting hazard associated with a defined exposure to a single toxicant, all toxicity data should be used along with the ADI. This dictates that the data need to be rated for severity of effect and that the exposure level and duration be converted to equivalent human values. This procedure allows all available toxicity data on a chemical to be used in predicting the results of a given exposure to humans. One method for incorporating all the data in a predictive assessment is demonstrated by Figure 2, a graph of study dose and duration versus effect severity.

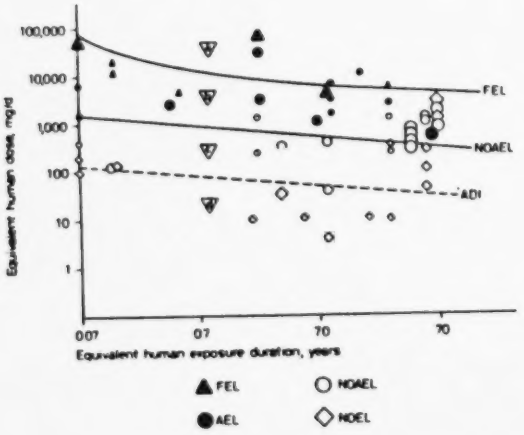

FIGURE 2. EFFECT-DOSE-DURATION PLOT FOR ALL RELEVANT HUMAN ANIMAL ORAL TOXICITY DATA FOR METHOXYCHLOR (15).

Figure 2 represents a visual review of all available toxicity data for methoxychlor. Each symbol represents an observed severity of effect placed at the corresponding exposure duration and average daily dose of each experiment. The human equivalent dose rate has been estimated by the mg/surface area equitoxicity model, and the exposure duration has been converted based on the fraction of lifespan. The larger symbols indicate greater confidence in the data. Depending on the consistency of the pattern, a statistical or judgmental (eye-fit) approach is used to estimate toxic potential for varied exposure levels and durations. In Figure 2, the judgmental approach has been used to divide the dose/duration plane into areas expected to cause either: (a) gross toxicity or death; (b) adverse effects; (c) non-adverse effects; or (d) no effects (15).

MIXTURES OF CHEMICALS OR MIXED EXPOSURES

Most instances of environmental contamination involve concurrent or sequential exposures to a variety of compounds that may induce similar or dissimilar effects over exposure periods ranging from short-term to lifetime. In some instances, the mixtures are highly complex consisting of scores of compounds that are generated simultaneously as by-products from a single source or process (e.g., coke oven emissions and diesel exhaust). In other cases, complex mixtures of related compounds are produced as commercial products (e.g., PCBs, gasoline and pesticide formulations) and eventually released to the environment. Another class of mixtures, simple mixtures, consist of compounds (often unrelated chemically or commercially) which are placed in the same area for disposal or storage, eventually coming into contact with each other and being released as a mixture to the environment. The information available for risk assessment varies considerably for different mixtures. Occasionally, the chemical composition of a mixture is well characterized, levels of exposure to the population are known, and detailed toxicologic data on the mixture are available. Most often, not all components of the mixture are known, exposure data are uncertain, and toxicologic data on the known components of the mixture are limited. Nonetheless, the government agency may be required to take action because of the number of individuals at potential risk or because of the known toxicologic effects of certain compounds that have been identified in the mixture (18).

It is generally recognized that toxicant interactions may occur during any of the toxicologic processes that take place with a single compound: absorption, distribution, metabolism, excretion, and activity at the receptor site(s). In addition, compounds may interact chemically, producing new reactive species with different spectra of biological effects.

Because of the uncertainties inherent in any approach to predicting the magnitude and nature of toxicant interactions, any assessment of health risk from chemical mixtures must include a thorough discussion of all assumptions. No single approach can be used for risk assessment of multiple chemical exposures; however, general guidelines can be recommended depending on the type of mixture, the availability of toxicity data on the mixture or similar mixtures and on the known interactions among its components, and the quality of exposure data. For the present, emphasis must be placed on flexibility, judgment, and clear articulation of all assumptions and limitations of approach to the risk assessment of these mixtures (18).

Table I outlines a procedure for assessing the risks from chemical mixtures. This recommended procedure is taken from a draft of EPA's "Guidelines for Health Risk Assessment of Chemical Mixtures" that reflects revisions from the proposed guidelines published in January, 1985. This current draft is not final and should not be construed as EPA policy.

The flow chart shows progressively what approach to take in assessing the risk of chemical mixtures based on available data. In general, if there is information on the mixture in question or on similar mixtures, then the preferred approach is to use these data over any other. The less desirable, but still useful approach, is to utilize analysis of the toxicity of each component, including any knowledge on interactions. Table 2 suggests that if similar effects are not present, then dose addition should not be used. With a mixture containing relatively few chemicals and no interaction data, an approach based on dose or response addition may be used as a rough approximation. Although the experimental support for additive models is not conclusive, it is suggestive. Several studies have demonstrated that dose additive models often predict acute toxicity reasonably well for mixtures composed of a variety of both similar and dissimilar compounds (6,11,12).

The problem of multiple toxicant exposure has been addressed by the American Conference of Governmental Industrial Hygienists (1), the Occupational Safety and Health Administration (10), the World Health Organization (20), and the National Research Council (8,9). Although the focus and purpose of each group was somewhat different, all groups that recommended an approach elected to adopt some type of dose additive model. Nonetheless, dose additive models are not the most biologically plausible approach if the compounds do not have the same mode of toxicologic action. Consequently, depending on the nature of the risk assessment and the available information on models of action and patterns of joint action, the most plausible model consistent with available experimental data should be used. (18).

Depending on the route of exposure and media of concern, the approach and the associated no-effect levels may be expressed in a variety of ways such as Acceptable Daily Intakes (ADIs), levels associated with specific

TABLE I. RISK ASSESSMENT APPROACH FOR CHEMICAL MIXTURES*(19)

1. Assess the quality of the data on interactions, health effects and exposure.

   a. If adequate, proceed to Step 2
   b. If inadequate, proceed to Step 14.

2. Health effects information is available on the chemical mixture of concern.

   a. If yes, proceed to Step 3.
   b. If no, proceed to Step 4.

3. Conduct risk assessment on the mixture of concern based on health effects data on the mixture. Use the same procedures as those for single compounds. Proceed to Step 7 (Optional) and Step 12.

4. Health effects information is available on a mixture that is similar to the mixture of concern.

   a. If yes, proceed to Step 5.
   b. If no, proceed to Step 7.

5. Assess the similarity of the mixture on which health effects data are available to the mixture of concern, with emphasis on any differences in components or proportions of components, as well as the effects that such differences would have on biological activity.

   a. If sufficiently similar, proceed to Step 6.
   b. If not sufficiently similar, proceed to Step 7.

6. Conduct risk assessment on the mixture of concern based on health effects data on the similar mixture. Use the same procedures as those for single compounds. Proceed to Step 7 (Optional) and Step 12.

7. Compile health effects and exposure information on the components of the mixture.

8. Derive appropriate indices of acceptable exposure and/or risk on the individual components in the mixture. Proceed to Step 9.

9. Assess data on interactions of components in the mixtures.

   a. If sufficient quantitative data are available on the interactions of two or more components in the mixture, proceed to Step 10.
   b. If sufficient quantitative data are not available, use whatever information is available to qualitatively indicate the nature of potential interactions. Proceed to Step 11.

Table I (cont'd)

10. Use an appropriate interaction model to combine risk assessments on compounds for which data are adequate, and use an additivity assumption for the remaining compounds. Proceed to Step 11 (optional) and Step 12.

11. Develop a risk assessment based on an additivity approach for all compounds in the mixture. Proceed to Step 12.

12. Compare risk assessments conducted in Steps 5, 8 and 9. Identify and justify the preferred assessment, and quantify uncertainty, if possible. Proceed to Step 13.

13. Develop an integrated summary of the qualitative and quantitative assessments with special emphasis on uncertainties and assumptions. Classify the overall quality of the risk assessment. Stop.

14. No risk assessment can be conducted because of inadequate data on interactions, health effects or exposure. Qualitatively assess the nature of any potential hazard and detail the types of additional data necessary to support a risk assessment. Stop.

*Note that several decisions used here, especially those concerning adequacy of data and similarity between two mixtures, are not precisely characterized and will require considerable judgment.

Margins of Safety (MOS), or acceptable concentrations of a pollutant in various media. For example, an index for multiroute exposure based on the ADI is:

$$HI_C = E_O/ADI_O + E_I/ADI_I + E_D/ADI_D \qquad (6)$$

where E is equal to exposure expressed in units of daily intake. The subscripts denote exposure route, i.e., O = oral, I = inhalation, and D = dermal. For example, E_I and ADI_I may be defined in terms of air concentration. This approach is taken where route specific "virtually safe" intake rates or practical thresholds are estimated. The contribution of each route is added to estimate the total hazard index of a single chemical. Naturally, this approach is most appropriate when route-specific criteria i.e based on systemic effects not related to portal of entry.

In order to compare total chemical exposure to an ADI value, exposure in units of media concentration must first be converted to an absorbed mg/day dose. For example:

water exposure level (mg/l) x water consumption (l) x absorption coefficient = water exposure (mg/day); or

air exposure concentration (mg/m^3) x daily ventilation volume (m^3) x absorption coefficient = air exposure (mg/day).

Assuming that the circulating blood level is responsible for the effects, then the ADI for any route may be used. The circulating threshold can be expressed in terms of any ADI with its corresponding absorption coefficient:

$$\text{Circulating Threshold} = (ADI_O)(a_O) = (ADI_I)(a_I) = (ADI_D)(a_D) \quad (7)$$

A single chemical Hazard Index for all exposure routes would be as follows:

$$HI_C = \frac{(E_O)(a_O)+(E_I)(a_I)+(E_D)(a_D)}{(ADI_J)(a_J)} \quad (8)$$

where the E_J can represent either oral, inhalation or dermal.

As an example, to estimate a total hazard index across one route, in this case inhalation, we would use the inhalation ADIs and inhalation exposures for each chemical:

$$HI_T = \frac{E_1}{ADI_1} + \frac{E_2}{ADI_2} + \ldots + \frac{E_N}{ADI_N} \quad (9)$$

The following equation can be used to determine the simple sum of the route indices, as in Equation 6, or it can be based on the absorbed levels, as in Equation 8.

$$HI_T = HI_1 + HI_2 + \ldots + HI_N \quad (10)$$

In the case of carcinogens, a similar additive approach can be used, except that instead of ADIs, doses corresponding to fixed risk levels such as 10^{-5} are used for each chemical.

The Hazard Index allows a qualitative estimate of whether or not a hazard may exist, i.e., a Hazard Index greater than 1 for either a single chemical across routes or for a group of chemicals determined to have potentially additive effects would qualitatively indicate a potential for hazard and suggest further investigation.

In order to quantitatively estimate hazard, one conceptually simple approach is response addition in which the correlation of individual responses within the population is assumed to be zero. The formula for predicting the total expected response (P_T) from exposure to two chemicals, using this assumption, can be expressed as: $P_T = P_1+P_2 (1-P_1)$. This equation can be generalized for any number of chemicals, as:

$$P_T = 1 - \prod_{i=1}^{n} (1-P_i) \quad (11)$$

For example, using this equation, the total incidence based on all adverse responses (PC_i) from each of five chemicals is given in the last column of Table II, and the total incidence for each adverse effect caused by the combination of chemicals (PE_i) is given in the last row of Table II. In this theoretical case, each of the five chemicals in the table exhibited two types of adverse responses (15).

TABLE II. EXAMPLE OF ASSESSMENT OF MULTIPLE TOXICANT EFFECTS RISK ASSESSMENT

Chemical Compound	Effects of concern						
	A	B	C	D	E	F	PC_i
I	$2x1-^{-2}$			$8x10^{-4}$			$2.08x10^{-2}$
II		$3x10^{-3}$			$1x10^{-3}$		$4.00x10^{-3}$
III			$4x10^{-2}$			$7x10^{-3}$	$4.67x10^{-2}$
IV	$5x10^{-3}$			$9x10^{-3}$			$1.39x10^{-2}$
V		$6x10^{-4}$				$6x10^{-3}$	$6.60x10^{-3}$
PE_i	$2.49x10^{-2}$	$3.60x10^{-3}$	$4x10^{-2}$	$9.79x10^{-3}$	$1x10^{-3}$	$1.30x10^{-2}$	$P_T = 8.9x10^{-2}$

Source: Adapted from Stara, et al., 1985.

The calculation of PE_i is a straightforward use of the above equation. The calculation of PC_i, the total incidence of adverse responses caused by each chemical, is somewhat different in that the assumption is that the separate effects induced by a given chemical are independent of one another. For some combinations of effects (e.g., increased liver weight, MFO induction, proliferation of SER in liver cells) this assumption obviously will be invalid. For such cases, it may be more reasonable to assume that the correlation of tolerances approaches unity (15).

Accepting for the moment that the responses of concern have been selected so that the assumption of independence among responses is reasonable, the total incidence based on all adverse effects from all chemicals (P_T) can be calculated from equation 11, substituting PE_i for P_i. The use of equation 11 is best justified when overall risks are small, and may be better justified for calculation of cancer risk than of toxic risk. However, where multiple effects in the same individual are judged to be significant, their probability can be easily calculated separately and expressed as an additional factor to be considered (15).

While this approach is conceptually simple, it is predicated on the ability to estimate response rates for the spectrum of effects associated with the individual chemical components. Dependent upon the data base available for the individual chemicals and the effects of concern, this may or may not be possible.

With each risk assessment of a chemical mixture there must be a thorough discussion of related uncertainties. They should be clearly discussed and the overall quality of the risk assessment should be determined based on an expression of the degree of confidence in the quality of the data on interaction, health effects and exposure.

DISCUSSION AND CONCLUSION

The various issues in environmental health dealt with in this paper need to be tied together in order to be understood by scientists who are not intimately familiar with risk assessment procedures as they relate to the implementation of environmental laws. The short discussion dealing with potential contamination of drinking water supplies in the U.S. is important because of the present emphasis by the Agency on ground water contamination. It appears that once an aquifer is contaminated by various toxic compounds it is much more difficult to develop appropriate controls than it is for

surface water pollution. Of course, a possibility exists that we just know much more about controlling contamination of surface water than ground water, and that it will take a few years before we have accumulated the knowledge and experience to deal with ground water contamination in a similar, rather satisfactory, fashion. Up to now, risk assessments for water pollutants (and other media) have addressed single chemicals. In order to understand the approaches being used for chemical mixtures, the single chemical assessments as they relate to a particular environmental medium have to be reviewed.

The Office of Drinking Water of the U.S. EPA has established in their risk assessment documents five levels to control adverse effects in the population due to drinking water. They are: 24-hour health advisories for 10 kg children and 70 kg adults; 10-day health advisories (10 kg and 70 kg); and a chronic effect criterion to control life-long exposure to pollutants in adult populations. Currently, all the values are determined for single chemicals. However, as discussed in the body of the paper, when we deal with hazardous waste sites, water reuse situations, or instances of combined effects of various air pollutants, we must consider that the populations are exposed to mixtures of chemicals. On that basis, we must develop testing procedures that are less time-consuming than standard bioassays, and yet, are satisfactory from a standpoint of data requirements for risk assessment procedures.

Many of the approaches described in this paper do not include the full range of issues typically addressed in health risk assessments performed by EPA. Normally such reports represent a detailed consideration of a pollutant's chemical and physical properties and a description of its behavior both physiologically and environmentally. Perhaps most important is the practice of presenting risk-specific intake levels for carcinogens and acceptable daily intakes for systemic toxicants in such a way as to fully describe all assumptions and uncertainties associated with these quantitative estimates. Furthermore, this process always entails scientific peer and policy review.

It is important to distinguish between hazard and risk assessment. Hazard assessments represent a primarily qualitative characterization of the spectrum of effects associated with exposure in addition to the parameters discussed above. Risk assessments, on the other hand, are usually based on the hazard assessment (4) as it relates to the exposed population, e.g., comparison of exposure to acceptable daily intake. Ideally, the assessment predicts the incidence of effects in an exposed population with all assumptions and uncertainties clearly articulated.

A primary problem encountered in risk assessment is defining risk at the low exposure levels typical of environmental human exposures. Despite data gaps on chemical toxicity not only for dose (in this instance low dose) but for route, duration and species of concern, there is often a real and/or perceived need to characterize risk. This need for characterization is not only for specific chemicals, but for different combinations of chemicals, multimedia exposures, and different endpoints of concern. This characterization effort is contingent upon biologically-based inference and extrapolation to develop a working hypothesis formulated to project risk. (4). This type of assessment effort is not intended to be in lieu of bioassay assessments, but rather to be complementary to bioassays. These factors are important for risk assessment as opposed to risk management issues such as regulatory impact analysis or cost benefit analysis.

This brief overview of current approaches to risk assessment of chemical mixtures and the related methodologic developments cannot fully reflect the extent and the complexity of the efforts required for these tasks. While some of the new developments related both to individual systemic toxicants and chemical mixtures, such as an improved approach to interspecies dose conversion, have been in progress for several years. Others, such as methodologies for partial lifetime health risk evaluation and the determination of sensitive population subgroups, are relatively recent. The proposed guidelines for health risk assessment of chemical mixtures (50 FR 1170) attempt to address the issues briefly discussed here, to assure a consistent approach to assessing mixtures and suggest promising areas of future research. Much effort is needed both in the area of improved risk assessment methodology as well as in the area of toxicology and validation of the theoretical approaches. It is hoped that overviews such as this paper will stimulate the necessary research so that improved data and mechanistic theories can increase the reliability and accuracy of predictive toxicology. The main point to be made, however, is that the Agency is making every reasonable effort to improve its risk assessment approach and will continue to do so.

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Dose-Response Analysis of Heavy Metal Toxicants in Man: Direct in vivo Assessment of Body Burden

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ABSTRACT

Differences in uptake, metabolism, and excretion of heavy metals makes selection of a suitable biological media as a monitor of body burden very difficult. Exposure assessments based on body fluid levels can provide, at best, only general population estimates. The most frequently monitored media are blood, urine, nail or hair clippings, sweat, and saliva. Unfortunately each of these tissues can be influenced by recent exposure conditions and are not accurate indices of the total dose or body burden. Direct in vivo measurements of body burden in humans, however, have recently been performed. This nuclear technique has focused on the measurements of kidney and liver cadmium (Cd) by neutron activation analysis and bone lead (Pb) determinations using x-ray fluorescence. The dose-response relationship for renal dysfunction based on the direct in vivo body burden for Cd is presented. The most probable Cd value for the kidney associated with renal impairment is approximately 35 mg. Approximately 10% of thesubjects with 20 mg Cd in the kidney will have moderately elevated β_2-microglobulin, an early indicator of potential renal functional changes.

INTRODUCTION

There is little doubt that significant adverse health effects are evident for high exposures to heavy metals (16,21,28). Animal studies have usually been the source of this information. In many cases these studies have been performed in animal species pre-selected for their enhanced response to a particular adverse effect, independent of the exposure agent. The doses used in toxicological studies may be much higher than those observed even in the most significant of industrial exposures or accidents. Extrapolation of these experimental findings to humans, therefore, becomes difficult. Much less is even known about the effects of low level chronic exposure or "environmental" exposure to heavy metals.

Two basic parameters, however, must be obtained in order to investigate dose-response or dose-effect relationships. These are (1) an adequate quantification of the true dose and (2) identification of the biological response. The second requirement has generally received the most research effort. Measurements of the adverse effects following an exposure can be performed without knowing the body burden or true dose to the target organ. Subtle physiological and biochemical changes, previously undetected, are becoming apparent as more sophisticated